REMARKS/ARGUMENTS

With this amendment, claims 10-12, 18-22, 47 and 50-51 are pending. Claims 29-46 are withdrawn. Claims 1-9, 13-17, 23-28, 48-49 and 52 are cancelled. Applicant's previous amendment in response to a May 15, 2006 Office Action was not entered. Therefore, for convenience, the Examiner's rejections are addressed in the order presented in the May 15, 2006 Office Action.

Applicants thank Examiner Grun for his time in conducting a telephonic interview on Friday, February 9, 2007. Claim language for the pending and withdrawn claims was discussed. Agreement was reached and is reflected in the attached claim listing.

I. Status of the claims

Claims 10 and 22 are amended to recite an isolated or purified antibody. Support for this amendment is found throughout the specification, for example, at page 11, lines 10-11. Claims 10, 22 and 47 are amended are amended to recite that the antibody binds to a native equine IgE protein. Support for this amendment is found throughout the specification, for example, at page 24, lines 6-15. Claims 11, 12, 50, and 51 are amended to recite that the antibody is polyclonal or monoclonal. Support for this amendment is found throughout the specification, for example, at page 14, line 1 through page 15, line 12. These amendments add no new matter.

II. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 10-12, 14, 17-24, 26, and 47-52 are rejected because the specification allegedly does not describe the claimed subject matter in a manner to convey to those of skill that the inventors had possession of the invention at the time of filing. In order to expedite prosecution, the claims are now directed to antibodies that bind to SEQ ID NO:5. In view of these amendments, withdrawal of the rejection for alleged lack of written description is respectfully requested.

III. Rejections under 35 U.S.C. §112, second paragraph

Claims 22-24, 26, 27, 50 and 51 are rejected for alleged indefiniteness. Claims 22-24, 26, and 27 re rejected for alleged improper Markush language. In order to expedite prosecution, the claims are amended and are no longer Markush claims. Claims 50 and 51 are rejected for alleged improper dependence from claim 10. In order to expedite prosecution, claims 50 and 51 no longer depend from claim 10.

IV. Rejections under 35 U.S.C. §101

Claims 48 and 50 are rejected as allegedly directed to non-statutory subject manner. In order to expedite prosecution, claim 48 is cancelled and claim 50 now depends from an independent claim that recites an isolated or purified antibody.

V. Rejections under 35 U.S.C. §102(b)

Claims 10-12, 14, 15, 17-19, 22-24, 26, 27 and 47 are rejected as allegedly anticipated under 35 U.S.C. §102(b) by Halliwell *et al.* in light of Watson *et al.* To the extent the rejections apply to the amended claims, Applicants respectfully traverse the rejections. To anticipate a claim, a reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found...in a single prior art reference." *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Thus, in order to anticipate, the cited reference must contain every element of the claims at issue. The cited references do not.

The amended claims are directed to a genus of isolated or purified antibodies that bind to a specific 15 amino acid peptide (SEQ ID NO:5), a fragment of the equine IgE protein. Thus, the claimed antibodies can be considered a subgenus of the genus of antibodies that bind to full length equine IgE. The claimed antibodies also surprisingly bind to the native equine IgE protein. Halliwell *et al.* disclose antibodies to full length equine IgE, but fail to provide any disclosure of the full length amino acid sequence of equine IgE or much less the sequence of the SEQ ID NO:5 peptide. In order to make the claimed isolated or purified antibodies that bind to SEQ ID NO:5, the sequence of SEQ ID NO:5 had to be known. Moreover, The Federal Circuit

Court of Appeals recently ruled that antibodies to a particular antigen are sufficiently disclosed so long as the antigen is "fully characterized." *Noelle v. Lederman*, 68 USPQ2d 1508, 1514 (Fed. Cir. 2004). The court ruled that disclosure must meet the written description requirement for a protein or nucleic acid sequence, *i.e.*, a functional characteristic coupled with correlation between structure and function. *Id.* at 1513. Halliwell *et al.* do not provide any sequence information on the equine IgE protein and therefore do not disclose the fully characterized antigen, as required.

The Federal Circuit has repeatedly ruled that in order to anticipate an invention, a prior art reference must contain an "enabling disclosure." *In re Hoeksema*, 158 USPQ 596, 600 (CCPA 1968). The proper test of an enabling description in a publication cited under §102 is:

> whether one skilled in the art to which the invention pertains could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention on which a patent is sought. *Id.*, and *In re LeGrice*, 301 F.2d 929, 939 (C.C.P.A. 1962).

The claimed invention is a genus of antibodies that bind to SEQ ID NO:5, a peptide, *i.e.*, a chemical compound. Courts have developed a body of case law regarding the information required to provide an enabling disclosure of a chemical compound. In order to place a chemical compound in possession of the public, the disclosure must be such that one of ordinary skill in the art could at once envisage the compound. *In re Donohue,* 207 USPQ 196, 199 (Fed Cir. 1980) and *In re Petering,* 133 USPQ 275, 279-280 (C.C.P.A. 1962). In addition, the reference must disclose a method of making the compound. *In re Hoeksema*, 158 USPQ at 601.

First, Halliwell *et al.* fails to enable the claimed invention because it does not provide a method of making the claimed antibodies that bind to SEQ ID NO:5, *i.e.*, the antigen required to make the antibodies. The Federal Circuit has provided a legal standard for information necessary to conceive a method of making a nucleic acid, and, by analogy, the information necessary to disclose a method of making a protein. According to the Federal Circuit, both conception of a nucleic acid structure and a method of making a nucleic acid occur

simultaneously with disclosure of the DNA sequence. *See Amgen v. Chugai*, 927 F.2d 1200 (Fed. Cir. 1991); *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993); *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993); and *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995). Thus, in order to disclose a method of making a *specific* nucleic acid or genus of nucleic acids (or polypeptide(s)), a *specific* DNA sequence (or amino acid sequence)must be provided. Without disclosure of the amino acid sequence, the cited reference does not provide the required "enabling disclosure" for the sequence of the antigen and by extension for the claimed antibodies. Thus, Halliwell *et al.*'s failure to provide any amino acid sequence information for equine IgE, means that Halliwell *et al.* is not an enabling disclosure. The disclosure of the full length equine IgE sequence by Watson *et al.*, 12 years after the publication of Halliwell *et al.*, does nothing to correct the inadequate disclosure of Halliwell *et al.*

In view of the above amendments and remarks, withdrawal of the rejections for alleged anticipation is respectfully requested.

VII. Rejections under 35 U.S.C. §103(a)

Claims 10-12, 14, 15, 17-24, 26, 27 and 47 are rejected under 35 U.S.C. 103(a) as allegedly obvious over the combined teachings of Marti *et al.*, Griot-Wenk *et al.*, Watson *et al.*, and Lerner *et al.* To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP§2143. See also *In re Rouffet,* 47 USPQ2d 1453. The court in *Rouffet* stated that "even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination." *Rouffet* at 1459. The court has also stated that actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, or teaching, or motivation to combine must be "clear and particular." *In re*

Dembiczak, 50 USPQ2d 1614, 1617 (1999). The Office Action does not provide a prima facie case of obviousness.

The claimed invention, as discussed above, is a patentable sub-genus of the genus of antibodies that bind to the full length antibody protein. According to the MPEP at §2144.08, in order to establish a *prima facie* case of obviousness against a species of a chemical composition that is allegedly part of a disclosed genus, it is **essential** to find a motivation to make or suggestion to make the claimed species in view of the cited reference. However, no specific teachings directing those of skill to make native IgE-binding antibodies directed exclusively against SEQ ID NO:5 are found in the cited references. In particular, establishment of a prima facie case of obviousness is precluded by 1) the size of the genus disclosed in the prior art, 2) the lack of structural similarity between the genus and the claimed species, and 3) the inability of those to skill to predictably make isolated antibodies that recognize native equine IgE based on the cited references.

The cited references disclose either a fragment of the equine IgE protein (Marti *et al.*, 1997), or one of two version of the full length equine IgE protein (Griot-Wenk, *et al.*, 2000 citing Navarro, 569 amino acids and Watson *et al.*, 1997, 566 amino acids). Lerner *et al.* discloses methods to raise antibodies against linear peptides within a protein that recognize full length protein, and in some cases the native protein. Lerner *et al.* disclose that the antigenic peptides are selected after the an encoding DNA is isolated, that the peptides can be as small as 4-6 amino acids long, but are preferably 15 amino acids long or longer and that any area of the full length protein is a suitable starting point. See, *e.g.*, Lerner *et al.*, page 16, lines 13-20 and page 46, lines 33-34. No other teaching or direction is provided by Lerner *et al.* or the other references to guide those of skill to select particular amino acid sequences in any particular protein. Thus, in combination with Lerner *et al.* the other references teach generation of up to 565 different 4 amino acid peptides, 564 different 5 amino acid peptides, 563 different 6 amino acid peptides, 562 different 7 amino acid peptides, and so on up to, *e.g.*, 554 different 15 amino acid peptides. Assuming a total of 12 peptide groups from 4-15 amino acids long averaging 560 members per group, one of skill would learn from the combination of references to generate antibodies to 6720 peptides and screen them for 1) antigenicity and 2) ability to recognize native

equine IgE. This genus is not so small that the recited SEQ ID NO:5 sequence would be recognized immediately out of the 6720 peptides by those of skill and thus, those of skill would not be motivated by the cited references to select SEQ ID NO:5 as an antigen and arrive at the claimed antibodies.

The Office Action also appears to assert that allegedly small differences in peptide sequences, *e.g.*, a 15-mer versus a 5-mer that include the same sequence, will have little or no effect on the antibodies raised against the peptides. Office Action at page 5. However, the claimed antibodies must recognize a specific protein structure in order to recognize the native IgE protein. The US Patent Office has very consistently asserted that even the smallest change in an amino acid sequence, *i.e.*, a change to a single amino acid residue, can have a detrimental effect on a protein structure. *See, e.g.*, MPEP 2144.08 (II)(4)(c), *citing* Darnell *et al.*, *Molecular Cell Biology* 51 (2d ed. 1990). Thus, the Office Action's position on the structural relationship between peptides with even a single amino acid difference is inconsistent with US Patent Office procedures and should be withdrawn. Therefore, any alleged structural similarity between peptide antigens is not sufficient to provide motivation for those of skill to select SEQ ID NO:5 as an antigen to arrive at the claimed antibodies.

The Office Action also overestimates the predictability of designing an antigen that will recognize a native protein. For example, at page 5 the Office Action indicates that a 5-6 amino acid epitope found with SEQ ID NO:5 is sufficient to provide antibody binding to a native protein. Lerner *et al.* demonstrates that this is not correct, using antibodies generated against peptide fragments of the hepatitis B antigen (HbAg) as an example. See, *e.g.*, Lerner *et al.* at page 55, line 29 through page 56, line 1. Peptides 6 and 4 induced antibodies that bind native HbAg. However, six-mer subfragments of peptides 6 and 4 did not raise antibodies that bind native HbAg. Thus,Lerner *et al.* teaches that the identification of a peptide that generates antibodies that bind a native protein is not predictable. Lerner *et al.* also found that the ability of some peptides to raise antibodies was also dependent on the pH of the buffer used for injection. See, *e.g.*, Lerner *et al.* at page 56, lines 6-16. Arguably, Watson *et al.* and Marti *et al.* followed the procedure of Lerner *et al.* in generating antibodies against peptides of the equine IgE protein. However, neither reference disclosed peptides that recognize SEQ ID NO:5 or peptides that

necessarily raise antibodies that bind the native IgE protein. Thus, experimental evidence in the cited references demonstrates that identification of peptides that bind to a native protein based on sequence alone is not predicable for those of skill.

The Office Action also improperly applies an "obvious to try" standard to the pending claims. Applicants have provided the sequence of a 15 amino acid peptide from the 566 amino acid equine IgE heavy chain protein and demonstrated that antibodies directed against that peptide surprisingly recognize the native IgE protein. The Office Action alleges that the minimal epitope for antibody binding is 5-6 amino acids and that Watson *et al.* teach the recited sequence. Office Action at page 5. However, Watson *et al.* teaches the full length sequence of the equine IgE protein and does not direct one of skill to the specifically recited peptide of SEQ ID NO:5. None of the other cited references direct one of skill to the recited peptide, either alone or in combination with Watson *et al.* According to the MPEP at §2145 the following "obvious to try" standard is not correct,. "In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful...." As discussed in detail above, assuming antibody binding sites from 4-15 amino acid long, and absent direction from any of the references, those of skill would have had to synthesize 6720 4-15 amino acid peptides from equine IgE protein, generate antibodies against them, and test the antibodies for ability to recognize native IgE protein. Lerner *et al.*, even if combined with the cited sequences of the equine IgE protein, does not provide any direction to the recited SEQ ID NO:5. Thus, it appears that the Office Action has applied an incorrect "obvious to try" standard in the §103 rejection, which should thus be withdrawn.

Finally, Lerner *et al.* teaches away from its combination with the other references to allegedly arrive at the claimed invention. Lerner *et al.* disclose generation of antibodies raised against peptides of the HbAg and specifically advise against using a region of the protein that does not have a consensus sequence among various published nucleotide sequences. With the last response, Applicants submitted an alignment of IgE protein sequence of Navarro *et al.* used by Marti *et al.* to generate peptides and the IgE sequence of Watson *et al.* used by the inventors

to generate antigenic peptides. The two amino acid sequences differ at many sites, including the sequence used by the inventors to make SEQ ID NO:5 indicating a lack of consensus sequence data at that portion of the IgE protein. Thus, Lerner *et al.* teaches those of skill to avoid use of non-consensus sequences from the equine IgE protein, including SEQ ID NO:5, as an antigen for antibody production.

In view of the above amendments and remarks, withdrawal of the rejections for alleged obviousness is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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